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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,267	10/13/2000	Jeffrey Glenn	240042052403	1206

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MORRISON AND FOERSTER LLP
3811 VALLEY CENTER DR.
Suite 500
San Diego, CA 92130-3310

EXAMINER
BRUMBACK, BRENDA G

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

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09/687,267	10/13/00	GLENN J	240042052403

HM12/0801

PENG CHEN
MORRISON & FOERSTER LLP
12636 HIGH BLUFF DRIVE
SUITE 300
SAN DIEGO CA 92130-2071

EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1642	7

DATE MAILED: 08/01/01

Forwarded 1/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/687,267	Glenn
Examiner	**Art Unit**
Brenda Brumback	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 14, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *13-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. This action is responsive to the amendment filed 05/14/2001 with Exhibit A (the Glenn Declaration) and Exhibits B-M. Claims 13-21 are pending and under examination.

Information Disclosure Statement

2. The Supplemental Information Disclosure Statement filed 12/6/2000 is acknowledged. A signed copy is attached hereto. Additionally, submission of full-text articles for References 7, 30, 35-36, and 39 listed on the PTO-1449 submitted 10/13/2000 as Exhibits B-G is noted. The full-text articles have been considered.

Oath/Declaration

3. The Supplemental Declaration under 37 C.F.R. 1.67(c) filed 05/14/2001 is acknowledged.

Claim Objections

4. The objection to claims 13-21 as lacking proper introduction is withdrawn pursuant to applicant's amendment.

Claim Rejections - 35 USC § 112

5. The rejection of claims 13-21 under 35 U.S.C. 112, first paragraph, is maintained. The Glenn Declaration, applicant's arguments, and Exhibits B-M have been fully considered but they are not persuasive for the following reasons.

Applicant argues that the teachings of Benet regarding solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, and rate of excretion or clearance are not related to enablement of the presently claimed method, but rather are concerns and questions that are to be dealt with by regulating authorities and/or the treating physicians, as is stated in Ex parte Balzarani. Applicant further argues that in Ex parte Balzarani the court did not find the examiner's concerns regarding possible side effects occurring with anti-viral drugs to be particularly relevant to issues of utility or enablement.

Firstly, the present rejection under 35 U.S.C. 112, first paragraph, is based on teachings of unpredictability of *in vivo* anti-viral treatments in attaining effective concentrations of the drug at the target site, bioavailabilty of the drug at the target site, solubility in tissues, rate of excretion or clearance, and attainment of effective plasma concentrations, not simply the possibility of the occurrence of side effects. All of these teachings of unpredictability relate directly to enablement of the presently method, which is drawn to a method of treating a viral infection in a subject comprising administering an anti-viral agent selected from a peptide that mimics the amino acid sequence of a CXXX, XCXX, XXCX, or XXXC box in the viral protein; an inhibitor of enzymes

in the pathway of prenyl lipid synthesis from mevalonate; an inhibitor of a prenyl transferase; and a mimic of a prenyl group. Attainment of an effective concentration of the agent at the site of infection is not only relevant to enablement; it is fundamental. Secondly, in Ex parte Balzarini, the court held that when the references of record establish that persons skilled in the art would question the objective truth of utility for *in vivo* treatment based solely upon *in vitro* testing, declarations submitted for applicants showing only *in vitro* data establish, at most, that *in vitro* testing is a useful tool for screening potential anti-viral agents, but is not predictive of *in vivo* effectiveness (see Headnotes 2). The Glenn Declaration filed 05/14/2001 discloses exclusively *in vitro* results; there are no *in vivo* data. Regarding applicant's allegation that concerns regarding efficacy and toxicity of anti-prenylation treatment are to be dealt with by appropriate medical regulating authorities, in Ex parte Balzarini, the court held that the holding that results of *in vitro* tests do not establish utility for *in vivo* treatment does not equate to a holding that human clinical testing is the only acceptable proof of utility, but rather reflects that applicant has failed to rebut the showing that those skilled in the art would not associate successful *in vitro* results with successful *in vivo* treatment (see Headnotes 3).

Applicant argues that the concern on the toxicity or lack of specificity of the claimed anti-prenylation treatment, have been dealt with and points to Exhibits A (the Glenn Declaration) and B (Glenn et al, Journal of Virology, 1998) in support of this argument. This argument, however, is not persuasive because the data presented in the Glenn Declaration are exclusively *in vitro* data, as well as are the data presented in the article labeled Exhibit B.

Applicant argues that Rice is irrelevant to the present methods because Rice reviews discovery and *in vitro* development of AIDS antiviral drugs as biopharmaceuticals. Even though Rice does disclose targets for antiviral therapy that are not the same as that of the present invention, the relevant teaching in Rice is that drug discovery for viral diseases is replete with failures (page 390, third paragraph, first sentence). This teaching of unpredictability is clearly not limited to only HIV, but applies to all viruses. The present claims are drawn to a method of treating viral infection in a subject. Thus, the teachings of unpredictability found in Rice relate directly to the presently claimed method.

Applicant argues that the present application does not contain teachings regarding the *in vivo* efficacy and toxicity of tetrapeptides because one skilled in the art could make and use them for *in vivo* therapy based on the disclosure of the present application coupled with information known in the art without undue experimentation. This argument is not persuasive, however, because Gibbs teaches that tetrapeptide inhibitors may require "**significant** modification before they are pharmacologically useful" (emphasis added). Given the teachings of unpredictability in the art and absent disclosure or guidance in the instant specification which overcomes these teachings, one of skill in the art would not be able to practice the claimed invention absent undue experimentation. While experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (MPEP 2164.06), the experimentation required in the present case is not routine and there is no guidance in the specification as to the direction in which the

experimentation should proceed. General teachings found in Gilman regarding techniques for developing therapeutics are insufficient to establish the experimentation required as merely routine.

Applicant argues that applicant has shown that BZA-5B and FTI-277 can effectively inhibit the production of HDV virions at a concentration that does not significantly affect overall cell metabolism. However, in the cited portion of the Glenn et al. reference (page 4 of the response), although Glenn et al. report no "gross cellular toxicity", they do report some inhibition of cell growth in the presence of high BZA-5B concentrations. Conventional wisdom would dictate that if cell growth is inhibited *in vitro*, that there is a significant likelihood of an adverse affect *in vivo*. Furthermore, interpretation of the data regarding FTI-277 presented in the Glenn Declaration is not clear-cut, as the legend Fig. 4 refers to colors in the graph, which graph was submitted in black and white. Additionally, the statement in the Glenn Declaration that "As shown in Figure 4, FTI-277 can effectively inhibit HDV virion production at a concentration that essentially does not affect general protein synthesis and overall cell metabolism" again suggests that there is some effect on protein synthesis and cell metabolism which may be significant *in vivo*. Even if the data presented demonstrated a complete lack of any effect on protein synthesis and cell metabolism *in vitro*, *in vitro* data is at best an initial screen. The results may not be the same *in vivo*. Applicant's claimed method is drawn to a method of treating a viral infection *in vivo*. Applicant's argument that Rightsel and Detroy are irrelevant because neither teaches treating viral infection is not persuasive because the relevant teachings are that inhibitors of protein prenylation

may be insufficiently soluble, unacceptably toxic, and/or carcinogenic. The reasons for administration of the compounds are irrelevant to the present grounds of rejection under enablement.

Applicant argues that the present specification teaches how the inhibitors may be administered. The portion of the specification referenced by applicant, however, is merely a disclosure of standard routes of administration of therapeutics in general. This is not persuasive because there are no teachings which provide guidance in overcoming the teachings of unpredictability found in the prior art of record. Regarding the absence of any working examples, while it is true that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation, such disclosure is absent from the present specification for the reasons outlined herein and in the previous Office action.

Applicant argues that mimics of a prenyl group encompass compounds which "behave like a prenyl group" but cannot be used as a prenyl group donor in a functional prenylation reaction and argues that in one aspect mimics of prenyl groups behave as competitive inhibitors of prenyl group donors. However, applicant then goes on to state that this description is for illustration only and that the meaning of mimics of a prenyl group should not be limited to such a competitive inhibitor. Applicant then cites other articles (Exhibits C, F, G, E, and D) of exemplary prenyl group mimics and states that "these prenyl group mimics are molecules with distinct structures" and are "a diverse group of molecules". These arguments are not persuasive because applicant

has failed to teach the metes and bounds of the recited mimics of a prenyl group in the context of the present invention and has failed to define a function which can be used to determine if a compound is encompassed within the recited group.. Absent such disclosure, the skilled artisan would be unable to practice the claimed invention absent undue experimentation.

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
July 26, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600